New Approach May Render Disease-Causing Staph Harmless

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A multi-institution collaboration between U.S. and Taiwanese scientists, including researchers at the University of California, San Diego (UCSD) School of Medicine and the Skaggs School of Pharmacy and Pharmaceutical Sciences, has uncovered a completely new treatment strategy for serious Staphylococcus aureus ("Staph") infections. The research, published February 14th in the online version of the journal *Science* (ScienceXpress), comes at a time when strains of antibiotic-resistant Staph (known as MRSA, for methicillin-resistant S. aureus) are spreading in epidemic proportions in both hospital and community settings.

The multi-institutional team exploited a chemical pathway that allows the Staph to defend itself against an immune response. The researchers showed that a compound called BPH-652 – originally designed to lower cholesterol – blocks a key enzyme in that pathway, weakening the Staph's defenses and allowing the body's immune cells to prevail against the infection.

A golden-colored pigment ("aureus" means golden in Latin) called a carotenoid gives the S. aureus bacterium its edge. The carotenoid acts as an antioxidant for the bacterium, allowing it to evade attack by the body's immune cells. By crippling production of the carotenoid, the compound strips the Staph of one of its key defenses.

Among the deadliest of all disease-causing organisms, Staph is the leading cause of human infections in the skin, soft tissues, bones, joints and bloodstream, and drug-resistant staph infections are a growing threat. By federal estimates, more than 94,000 people develop serious MRSA infections and about 19,000 people die from MRSA in the United States every year.

The new research builds on a 2005 discovery by scientists at UCSD, led by Victor Nizet, MD, professor of pediatrics and pharmacy, and George Liu, M.D., then a post-doctoral fellow at UCSD. That study showed that knocking out a gene for an enzyme in the chemical pathway that produced the Staph carotenoid reduced its virulence.

When he read about this finding, University of Illinois chemistry professor Eric Oldfield realized that the chemical precursors of the Staph carotenoid were identical to those that led to production of cholesterol in humans. Oldfield had spent decades exploring this pathway, which has

implications for the treatment of some cancers, as well as fungal and parasitic diseases. He noted that an enzyme in the human pathway, squalene synthase, was strikingly similar to one that led to the production of the carotenoid in Staph. He also knew that many compounds had already been developed to block the human enzyme.

"I thought there was a good chance that squalene synthase inhibitors developed early on as cholesterol lowering agents might also work on this other pathway," he said. "Current cholesterol-lowering drugs like statins work in a completely different way and would be ineffective."

The researchers began by testing dozens of new compounds for their activity against the Staph enzyme. This allowed them to narrow the field of potential candidates to eight. When they tested these drugs on Staph cells, they found that BPH-652 was the most effective at getting into the cells. A tiny dose impaired the cells' ability to produce the carotenoid. The cells, once golden, turned white.

"We have found that the same golden armor used by Staph to thwart our immune system can also be its Achilles' heel," said Nizet, who is also affiliated with the Skaggs School of Pharmacy and Pharmaceutical Sciences at UCSD.

Preliminary studies were conducted in the laboratories of Nizet and Liu, now an assistant professor of pediatrics at Cedar-Sinai Medical Center in Los Angeles. Exposure to BPH-652 also markedly reduced bacterial levels in a mouse model of severe Staph infection.

The key to the compound's success lies in the fact that the human and bacterial enzymes it targets are so similar.

Andrew Wang and his colleagues at Academia Sinica and the National Taiwan University used X-ray crystallography to determine the structure of the enzyme and how it interacts with the inhibitors. "Our structural studies pinpointed how these drug candidates bound to the bacterial enzyme to shut off pigment production," Wang said.

The new findings are particularly promising because BPH-652 has already been explored as a cholesterol-lowering agent in human clinical trials. The existing knowledge of its properties may reduce the cost and time required for development of BPH-652 as an anti-infectious disease therapy, according to the researchers.

"This research is an excellent example of how discoveries at the lab bench can lead to clinical advances," said Elias A. Zerhouni, MD, director of the National Institutes of Health (NIH), which supported the research. "By following their scientific instinct about a basic biological process, the researchers found a promising new strategy that could help us control a very timely and medically important health concern."

Additional contributors to the paper include Chia-I Liu and Wen-Yih Jeng, Academia Sinica, Taipei, Taiwan; Youngcheng Song and Fenglin Yin, University of Illinois at Urbana-Champaign; and Mary E.

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